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EXAMINER	
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ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,181	HILLEBRAND ET AL.	
	Examiner	Art Unit	
	CATHY K. WORLEY	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *5-9,11-26 and 28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 10, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed Oct. 28, 2009, has been entered.

2. Claim 30 has been newly added and is directed to the invention from Group II from the restriction requirement mailed on Mar. 31, 2009, which was not elected in the response filed on April 29, 2009, therefore it is withdrawn from consideration for being directed to a non-elected invention.

Claims 1-30 are pending.

Claims 5-9, 11-26, and 28-30 are withdrawn.

3. Claims 1-4, 10, and 27 are examined in the present office action.

Objections and Rejections that are Withdrawn

4. The objections to the specification for non-descriptive title and abstract and for improper use of trademarks are withdrawn in light of the Applicant's amendments to the specification, title, and abstract.

5. The objections to claim 2 are withdrawn in light of the Applicant's amendments to the claims.

6. The rejection of claims 1, 3, 4, 10, and 27 under 35 USC 112, 2nd paragraph, is withdrawn in light of the Applicant's arguments which were found to be persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 10, and 27 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Applicant's arguments in the response filed on Oct. 28, 2009, were fully considered but were not found to be persuasive.

The claims are broadly drawn to a method that utilizes "compound X" and "compound M" both of which comprise a "D-amino acid structure". The specification states that a D-amino acid structure is intended to include D-amino acids as well as analogues, derivatives, and mimetics of the D-amino acid that maintain the functional activity of the compound (see last paragraph on page 40 of the specification).

The essential feature of compound X is that it is phytotoxic against plant cells and can be metabolized by a D-amino acid oxidase into one or more compounds which are non-phytoxic or less phytotoxic than compound X (see part "ii" of claim 1). The essential feature of compound M is that it is non-phytotoxic or moderately phytotoxic against plant cells and can be metabolized by a D-amino acid oxidase into one or more compounds which are phytotoxic or more phytotoxic than compound M (see part "iv" of claim 1).

The Applicants describe D-alanine and D-serine as choices for compound X and D-isoleucine and D-valine as choices for compound Y (see Figure 1; and see first paragraph on page 32).

The Applicants do not describe any D-amino acids other than D-alanine and D-serine that are demonstrated to function as required for compound "X"; and they do not describe any D-amino acids other than D-isoleucine and D-valine that are demonstrated to function as required for compound "M". The Applicants do not describe any analogues, derivatives, and mimetics of D-amino acids that maintain the functional activity of the compounds.

The Applicants fail to describe a representative number of D-amino acid structures that can function as required for compound X and compound M. The Applicants only describe D-alanine and D-serine for compound X and D-isoleucine and D-valine for compound M. Furthermore, the Applicants fail to describe structural features common to members of the claimed genus of D-amino acid

structures. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for a compound to be phytoxic against plant cells, as required for compound X, and metabolized by a D-amino acid oxidase into one or more compounds which are non-phytoxic or less phytotoxic than compound X (see part "ii" of claim 1), it remains unclear what features identify a D–amino acid structure capable of such activity. Given the lack of description of the necessary elements essential for a compound to be non-phytotoxic or moderately phytotoxic against plant cells, as required for compound M, and metabolized by a D-amino acid oxidase into one or more compounds which are phytotoxic or more phytotoxic than compound M (see part "iv" of claim 1) it remains unclear what features identify a D–amino acid structure capable of such activity. Since the genus of D-amino acid structures that are capable of serving as compound X and compound M has not been described by specific structural features, the specification fails to provide an adequate written description to support the breadth of the claims.

D-amino acid structures can be analogues, derivatives, and mimetics of any D-amino acid (see last paragraph on page 40 of the specification). Therefore the genus of D-amino acid structures encompasses a very large number of molecules, many of which would not have the required phytotoxicity to plants and relief of phytotoxicity after metabolism by D-amino acid oxidase as required by compound X, and most of which were not in the possession of the applicant at the time of filing.

In addition, the genus of D-amino acid structures encompasses a very large number of molecules, many of which would not have the required lack of phytotoxicity and production of phytotoxic metabolite by D-amino acid oxidase activity as required for compound M, and most of which were not in the possession of the applicant at the time of filing. The Applicants have reduced to practice only two compounds for compound X (D-alanine and D-serine – see figure 4) and two compounds for compound M (D-isoleucine and D-valine – see figure 4). Accordingly, the specification fails to provide an adequate written description to support the genus of D-amino acid structures that can function as compound X and compound M as set forth in the claims. (See Written Description guidelines published in 2008 online at http://www.uspto.gov/web/menu/written.pdf).

APPLICANT'S ARGUMENT

The Applicant argues that the specification has described multiple possibilities for D-amino acid structures that can be used for compound X and compound M and that a patent preferably omits that which is well known to those skilled and already available to the public (see pages 14-16). This is not persuasive, however, because although the specification provides a list of possibilities for compound "X" and compound "M" on page 7, the lists include "derivatives" of D-amino acids; and the specification includes a prophetic list of possible derivatives (see page 40), none of which have been reduced to practice. With regard to that which is already known and available to the public, the Examiner is not aware of

any compounds that were publicly known at the time of filing to have the required function of compound X and compound M when acted on by D-amino acid oxidase in a plant, other than D-alanine, D-serine, D-isoleucine, and D-valine.

Because the genus of compounds that comprise a "D-amino acid structure" includes D-amino acids as well as analogues, derivatives, and mimetics of the D-amino acid that maintain the functional activity of the compound (see last paragraph on page 40 of the specification), this is a very large genus of compounds; and only two species of this genus have been reduced to practice for compound X and only two species have been reduced to practice for compound M. Therefore, with only two species reduced to practice, and a very large genus of molecules encompassed by the instant recitation, the written description requirement has not been met.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 10, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Signer et al (WO 01/96583; published on Dec. 20, 2001) in view of

Nasholm et al (WO 03/060133; published 0n July 24, 2003) and taken with the evidence of Stougaard, J. (The Plant Journal (1993) Vol. 3; pp. 755-761) and the evidence of Boeke et al (Methods in Enzymology (1987) Vol. 154; pp. 164-175). The Applicant's arguments in the response filed on Oct. 28, 2009, were fully considered but were not found to be persuasive.

The claims are directed to a method for producing a transgenic plant by transforming a plant cell with a nucleic acid encoding a D-amino oxidase and with a second nucleic acid conferring an agronomically valuable trait, and utilizing D-amino acid structures for both a positive selection step and a negative selection step, followed with breaking the combination between the two nucleic acids.

Signer et al teach a method of generating transgenic plants that utilizes both a positive selection marker and a negative selection marker in order to remove the selection markers from the resulting transgenic plants (see entire document). They outline a general protocol on page 11:

1) providing a DNA construct which comprises (a) direct repeats of a gene of interest at both ends flanking a positive selectable marker gene and a negative selectable marker gene and (b) one or more additional genes that flank either side or both sides of (a);

2) transforming cells by introducing the construct into the cells;

3) growing or culturing the cells on positive selective medium;

4) selecting the transformed cells having the genetic construct which grows on the positive selective medium;

5) transferring the cells to a negative selective medium;

6) growing or culturing the cells on the negative selective medium;

And

7) selecting those cells which grow on the negative selective medium.

Growth on the negative selective medium indicates that the selection markers have been excised.

Signer et al do not teach a sequence encoding a D-amino acid oxidase gene for use as either a positive or a negative selection marker; therefore, their construct is different the construct recited in the instant claims.

Nasholm et al teach that D-amino acids may be used for selection of transgenic plants expressing a D-amino acid metabolizing protein (see page 3). They teach that the D-amino acid metabolizing protein can be a D-amino acid oxidase (see line 21 on page 5). They teach that D-amino acid oxidase could be used as a positive selection marker with D-alanine and D-serine because D-amino acid oxidase would alleviate the toxicity caused by D-alanine and D-serine (see fourth paragraph on page 35. They also teach that D-amino acid oxidase could be used as a negative selection marker with D-isoleucine because applying D-isoleucine to plants expressing D-amino acid oxidase hindered the growth of the transgenic plant with no visible inhibitory effect on wild type plants (see first paragraph on page 36).

At the time the invention was made, it would have been obvious and within the scope of one of ordinary skill in the art to modify the teachings of Signer et al to utilize a construct encoding a D-amino acid oxidase as taught by Nasholm et al. One would have been motivated to do so, because Nasholm et al taught that one transgene (encoding D-amino acid oxidase) could be useful as both a positive and a negative selection marker, and therefore one would only require one transgene rather than two separate selectable marker genes.

This concept was generally known in the art as evidenced by the teachings of Stougaard (see entire article) and Boeke et al (see entire article). Stougaard teaches transgenic tobacco expressing a transgene encoding CodA which can be used for positive selection on N-(phosphonacetyl)-L-aspartate containing medium and can be used for negative selection on 5-fluorocytosine containing medium (see abstract). Boeke et al teach that the URA3 gene can be used in yeast as both a positive selectable marker and as a negative selectable marker (see figure 1 on page 166). It is common practice in yeast genetics to use a plasmid comprising the URA3 gene as a positive selectable marker by growing URA3- yeast on medium lacking uracil, therefore only the transformants carrying the URA3 gene are able to grow (positive selection). For a negative selection, the yeast would be plated on medium containing 5-FOA (5-fluoroorotic acid) (see Figure 1 on page 166).

Given the effect of different D-amino acids on transgenic plants expressing D-amino acid oxidase as taught by Nasholm et al, and given the success in using both

a positive selection and negative selection to identify transgenic plants and subsequently identify plants in which the marker has been excised that was taught by Signer et al, one would have had a reasonable expectation of success in combining the teaching to arrive at a method that utilizes D-amino acid oxidase as both a positive and negative selectable marker, as claimed in the instant application.

APPLICANT'S ARGUMENTS

The Applicant argues that Signer teaches two different selectable markers rather than teaching one marker that can be used for both positive and negative selection; and that Nasholm does not teach the use of D-amino acid oxidase for eliminating marker sequences from transgenic plants(see pages 17-18 of the response). This is not persuasive, however, because the rejection is based on the combination of references, not on either of these reference alone; and this is an attack on the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Applicant argues that nothing in Stougaard teaches the use of a dual-function marker for generating marker-free plants, and nothing in Signer teaches using a single selectable marker rather than using two markers (see third

paragraph on page 18 of the response). This is not persuasive, however, because the rejection is based on the combination of references, not on either of these reference alone; and this is an attack on the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Applicant asserts that they fail to see the relevancy of Boeke et al, because it relates to yeast systems rather than to transgenic plants (see paragraph bridging pages 18-19 of the response). To clarify, the Examiner will explain the relevancy: Boeke et al teach the use of one single selectable marker for both positive selection and negative selection in order to first select for transformants and then, subsequently select for transformants that have excised the marker (see figure 1 on page 166). This clearly points out that the idea of using one single selectable marker for both positive selection and negative selection in order to identify transformants, and subsequently identify transformants that have excised the marker is not a new idea in the field of molecular biology. This is why Boeke et al is relevant. The fact that it is in a yeast system is not important, because ordinary molecular biologists are well-read in tools that are utilized in yeast, bacteria, plants, insects, and mammalian expression systems.

The Applicant argues that the references teach away from the claimed invention; specifically that Signer utilized a separate positive marker (NPT) rather than relying on CodA for both positive and negative selection (see pages 19-20 of the response). This is not persuasive, however, because the claims are not directed to utilizing CodA for both positive and negative selection; the claims are directed to utilizing D-amino acid oxidase for both positive and negative selection. The method taught by Signer et al, taken together with Nasholm's teachings that D-amino acid oxidase can be useful for both positive and negative selection, and with Boeke's teaching that one can utilize one single marker for both positive and negative selection for the purpose of first identifying a transformant and second identifying transformants in which the marker has been excised, it would have been obvious to modify the teachings of Signer et al to utilize the D-amino acid oxidase marker taught by Nasholm et al. There is nothing in any of the references of record that teaches away from this combination.

The Applicant argues that there is no motivation for one of skill in the art to modify the teaching of Signer (see pages 20-21 of the response). This is not persuasive, however, because Nasholm teaches that D-amino acid oxidase can be used as both a positive and a negative marker; and Boeke et al demonstrates that this can lead to the use of one single marker for both selection of a transformant and identification of transformants from which the selectable marker has been excised. One of ordinary skill in the art would have appreciated the convenience of

utilizing one marker instead of two. The fact that Signer et al did not utilize CodA for both positive and negative selection does not teach away from the claimed invention, because the claimed invention is not directed to the use of CodA; it is directed to the use of D-amino acid oxidase. The fact that Signer et al used two markers instead of one does not take away from the teachings of Boeke et al that demonstrate the convenience of using one marker.

The convenience of using one marker instead of two is ample motivation for one of ordinary skill in the art to combine the teachings. However, even if there were no teaching, suggestion, or motivation to combine, *KSR* forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, - - USPQ2d - - , slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). Furthermore, in *KSR*, the court stated that "the analysis need not seek out precise teaching directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." The Court in *KSR* noted that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." 127 S.Ct. at 1742, 82 USPQ2d at 1396-7.

The Applicant argues that the modification suggested by the examiner requires a substantial reconstruction and redesign of the construct being modified

(see pages 21-22 of the response). Specifically, the Applicant argues that Signer teaches a construct using two selectable markers instead of using one and that this changes the basic principle under which the Signer construct was designed to operate (see second paragraph on page 22 of the response). This is not persuasive, however, because the Examiner has relied upon Signer et al for teaching the general idea that positive selection can be used to identify transformants, followed by negative selection to identify transformants from which the markers have been excised; and also Signer et al was relied upon to teach the specific method steps. Nasholm et al is relied upon to teach the construct encoding the D-amino acid oxidase and for teaching that D-amino acid oxidase can be used as both a positive selectable marker (with D-alanine or D-Serine) and a negative selectable marker (with D-isoleucine). Contrary to the Applicant's assertion, substituting the construct taught by Nasholm et al for the construct utilized by Signer et al does not require a substantial reconstruction of the method or principles taught by Signer et al.

The Applicant argues that combining Signer and Nasholm would still result in a construct that comprises two different selectable markers because there is no reason to eliminate the positive selectable marker (see page 23 of the response). This is not persuasive, however, because Boeke et al teach the idea of using one marker for both positive and negative selection, specifically for the purpose of first identifying a transformant followed by excision of the marker. The method steps

and the idea of using positive selection to identify a transformant followed by negative selection to identify a transformant from which the marker has been excised is taught by Signer et al; the use of D-amino acid oxidase as both a positive and negative selectable marker is taught by Nasholm et al; and the use of one single dual-function marker rather than two separate markers for the purpose of identifying a transformant followed by excision of selection marker is taught by Boeke et al. Therefore, the combination of references teaches the claimed invention.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cathy K. Worley whose telephone number is (571) 272-8784. The examiner is on a variable schedule but can normally be reached on M-F 10:00 - 4:00 with additional variable hours before 10:00 and after 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Cathy K. Worley/
Primary Examiner, Art Unit 1638